Clinical Performance of a Dermal Filler Containing Natural Glycolic Acid and a Polylactic Acid Polymer

Results of a Clinical Trial in Human Immunodeficiency Virus Subjects with Facial Lipoatrophy

[a]JORGE M. TAGLE, MD; [b]PEDRO CERVANTES MACCHETTO, MD*; [c]ROSA MARGARITA DURÁN PÁRAMO, MD*

[a]Plastic and Reconstructive Surgeon, International Board of Plastic, Aesthetic and Reconstructive Surgery, European Society of Plastic and Reconstructive Surgery Documentation; [b]Private Practice, General Hospital of Tijuana, Tijuana, Mexico; [c]Private Practice

ABSTRACT

Lipoatrophy is a condition that affects certain individuals, most commonly those who are infected with the human immunodeficiency virus.[1–3] Injectable fillers are used for the treatment of these dermal contour deformities to smooth dermal depressions formed by the loss of volume. These dermal fillers (also known as soft tissue augmentation devices) can correct contour deformities caused by lipoatrophy in patients who are human immunodeficiency virus positive or negative. The product used in this study is a patented, second-generation, injectable, dermal collagen stimulator that combines glycolic acid and polylactic acid. The glycolic acid used is not a polymer, but rather an acid derived from sugar cane. Its chemical structure corresponds to that of an alpha-hydroxy acid. Glycolic acid is a well-characterized agent that is present in a number of cosmetic products. Polylactic acid is a synthetic, biocompatible, biodegradable, inert, synthetic polymer from the poly a-hydroxy-acid family that is believed to stimulate fibroblasts to produce more collagen, thus increasing facial volume. Together, polylactic acid and glycolic acid act in concert to 1) stimulate collagen production and 2) hydrate the outer layers of the skin. A multicenter, clinical investigation authorized by the Mexican Secretariat of Health was conducted between September 20, 2002, and September 19, 2004. This clinical study was conducted in male patients between 32 and 60 years of age with lipoatrophy as a result of highly active antiretroviral therapy for human immunodeficiency virus infection. The study objective was to measure the improvement of contour deformities after the injection of a dermal collagen stimulator containing glycolic acid and polylactic acid. In addition to safety, this dermal filler was assessed when used to correct volume deformities caused by lipoatrophy in subjects who are human immunodeficiency virus positive. Thirty male subjects participated and were treated as follows: seven in two sessions, eight in three sessions, 14 in four sessions, and one in five sessions. Each treatment session was separated by approximately 20 days as per the manufacturer's instructions. The follow-up phase consisted of four observation periods over two years from the last injection. The primary efficacy endpoint was measurement of correction of human immunodeficiency virus highly active antiretroviral therapy induced facial lipoatrophy. Using a multipoint scale of facial divergence, correction was measured as a percentage of correction (diversion correction percentage) from baseline. A secondary endpoint was safety based upon the incidence and type of adverse events experienced. All 30 patients completed the active treatment phase with 100 percent (N=30) undergoing at least two treatments at Days 1 and 20 after entry into study. Seventy-four percent (n=23) underwent a third treatment at Day 60, and 50 percent (n=15) received a fourth treatment at Day 80. A single subject received a fifth treatment at Day 100. There were no serious adverse events and no adverse events noted during the study period. Histology through skin biopsy (2mm punch) was performed on 10 subjects, and all subjects had dermal skin thickness measured with ultrasound. Histology demonstrated a foreign body reaction with multinucleated giant cells with phagocytized lactate crystals. New collagen formation was demonstrated. United States measurements of dermal skin thickness increase ranged from 0.22cm to 0.37cm. All subjects were rated for expected injection events to include erythema, edema, ecchymosis, and hematoma. This dermal collagen stimulator containing glycolic acid and polylactic acid represents a tangible alternative in therapeutic and aesthetic medicine. More than four years of clinical trials have demonstrated that this dermal collagen stimulator helps to improve the exterior quality of the skin while restoring lost facial volumes. Patient satisfaction was high due to its effectiveness and long-lasting results, which in some cases have lasted more than two years. (*J Clin Aesthetic Dermatol.* 2010;3(2):42–47.)

DISCLOSURE: The authors report no relevant conflicts of interest. *At the time of the study, Dr. Macchetto was a Surgeon at the Hospital del Prado, Tijuana, B.C. Mexico, and Dr. Paramo was with Conasida, a Mexican government agency dedicated to the fight agains AIDS.

ADDRESS CORRESPONDENCE TO: Jorge M. Tagle, MD; E-mail: dr.jmtagle@hotmail.com

The basic design criteria for human use of injectable devices require sterility, biocompatibility, and the ability to demonstrate a controlled stability or degradation in response to specific biological conditions.[4] An ideal biodegradable device for medical applications has to have adequate mechanical properties to assimilate with the application. The device should not induce inflammation or other toxic responses and should be fully metabolized once it degrades. The patented dermal filler used in this study (DermaVeil) comprises glycolic acid (GA)[5] and polylactic acid (PLA) and meets these above-mentioned characteristics.[6,7] The clinical trials demonstrated that once this dermal filler has been implanted, no metabolic by-products were generated beyond the physiological accumulation of normal metabolites. The product did not stimulate local or systematic immune responses that would generate granuloma or neurosensory symptoms. Leukotaxis was selective and based on macrophages and occasionally on plasma B cells. The inflammatory phenomena was limited to foreign body reaction, which generated new collagen (neocollagenesis). The biological response decreased gradually in 12 to 14 months and disappeared on average in 18 months, with some recorded cases lasting over 24 months.

Both acids in the dermal filler are immunologically inert, biocompatible, absorbable, and degrade by hydrolysis. The component's degradation gives rise to a metabolite that is eventually reduced by the Krebs cycle to carbon dioxide and water, easily expelled by the body mainly through the respiratory system without histological evidence of the reaction. The degradation first occurs by diffusion of water into the material—initially into the more amorphous zones, followed by random hydrolysis, fragmentation of the material, and finally, an extensive hydrolysis accompanied by phagocytes, diffusion, and metabolism. Clinical trials have demonstrated that the combination of glycolic and polylactic acids notably improves the exterior quality of the skin diminishing its imperfections and restoring lost facial volume,[8] placing this medical device within the field of injectable devices used in dermatology and aesthetic medicine treatments.[9]

DermaVeil was approved by the Mexican Ministry of Health (SSA) in 2003 and has been commercially available since July 2006. The product is currently marketed outside the United States in Latin America as a second-generation dermal filler. DermaVeil can be reconstituted and used immediately. Thousands of patients have been treated in Latin America and most recently in the Far East. Patient satisfaction is high due to the device's effectiveness and long-lasting results. The product is pending registration in the United States.

METHODS

A government-controlled, multicenter, clinical investigation authorized by the Mexican Secretariat of Health was conducted between September 20, 2002, and September 19, 2004, with the participation of 30 male individuals between 32 and 60 years of age. Patient demographics are summarized in Table 1. The purpose of the study was to investigate the results obtained from the product's formula combination of glycolic and polylactic acids in the treatment of facial fat loss (lipodistrophy) and the damage it produces on the skin. Good Clinical Practices were observed throughout the investigation process, providing public guarantee that the rights, security, safeguard, and wellbeing of the participating subjects were protected in accordance with the spirit of the Declaration of Helsinki.

TABLE 1. Demographic characteristics

	MINIMUM	MAXIMUM	AVERAGE
Age (years)	32	60	42.66
Weight (kg)	52	88	67.16
Height (Mts.)	1.56	1.91	1.72

TABLE 2. Degree of lipoatrophy

		LIPOATROPHY DEGREE	
Session	Participants	Acute	Moderate
1st	30	14	16
2nd	30	14	16
3rd	23	14	9
4th	15	14	1*
5th	1	1*	

*During the investigation, it was decided that a patient with moderate lipoatrophy required a fourth intervention and a patient with acute lipoatrophy required a fifth intervention.

Only patients who suffered from the human immunodeficiency virus (HIV) were selected since the manifestation of severe lipoatrophy is characteristic of this disease. However, the function of injectable dermal fillers for the treatment of dermal contour deformities is to smooth dermal atrophy as a result of loss of facial volume.

Study subjects were chosen from a list of patients being treated at the Infectious Diseases Department of the General Hospital in Tijuana (Secretariat of Health—SSA) and from the Mexican Foundation for the Struggle against AIDS in Mexico City. The participants were selected by a committee, a government representative, the sponsor's medical representative, the independent medical auditor, and at least one member of the ethics committee (uneven number rule enforced).

Participants were required to have at least a six-month history of facial lipoatrophy caused by HIV and must have been on antiretroviral treatment and not received a dermal filling product during the six months prior to admission to the program. A clinical history of each participant was taken and each individual was examined before and after each session. Follow-up revisions were performed five days after the first session; 30, 90, and 180 days after the last session; and two years after the last session.

Of the 30 patients, 14 were diagnosed with acute lipoatrophy and 16 with moderate lipoatrophy. Patients were assigned between two and four sessions. During the

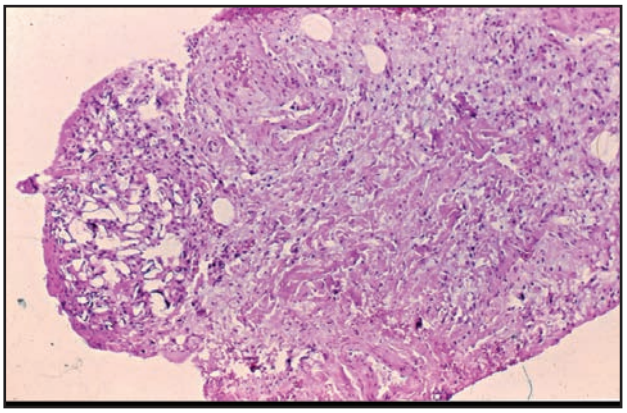


Figure 1a. Figures 1a–1d show the histopathology study in paraffin. Figure 1A (above): Hypodermis granuloma of foreign body type with phagocytized lactate crystals

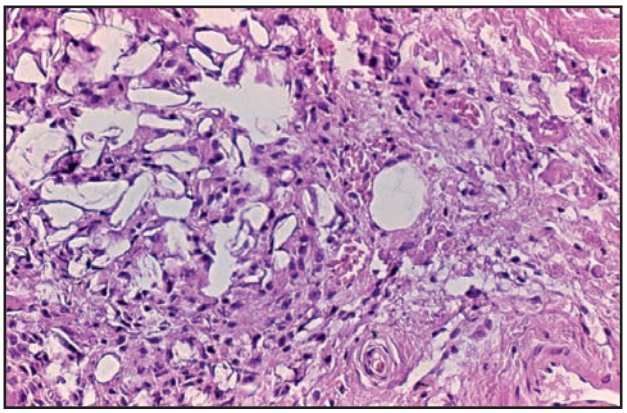


Figure 1b. Enlargement of previous slide: Multinuclear giant cells with phagocytized lactate crystals

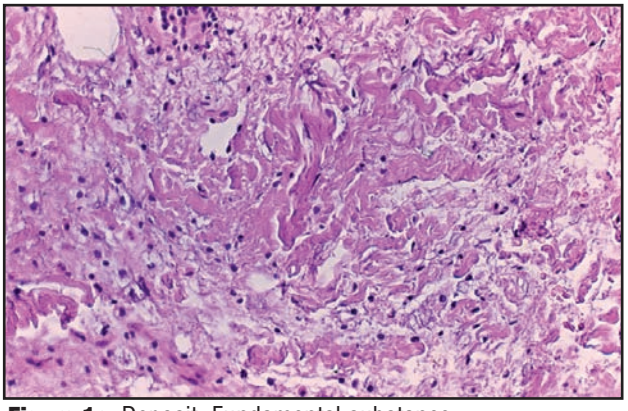


Figure 1c. Deposit. Fundamental substance

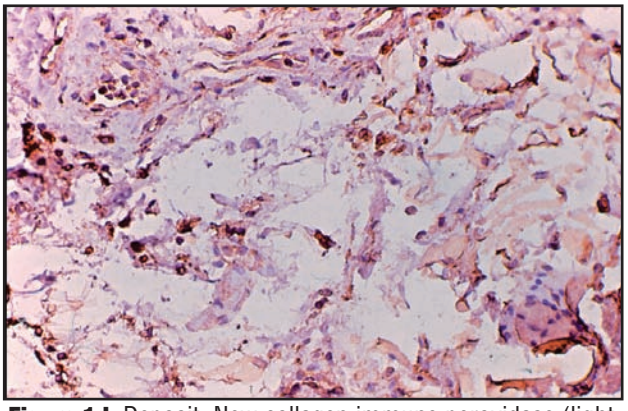


Figure 1d. Deposit. New collagen immune peroxidase (light brown)

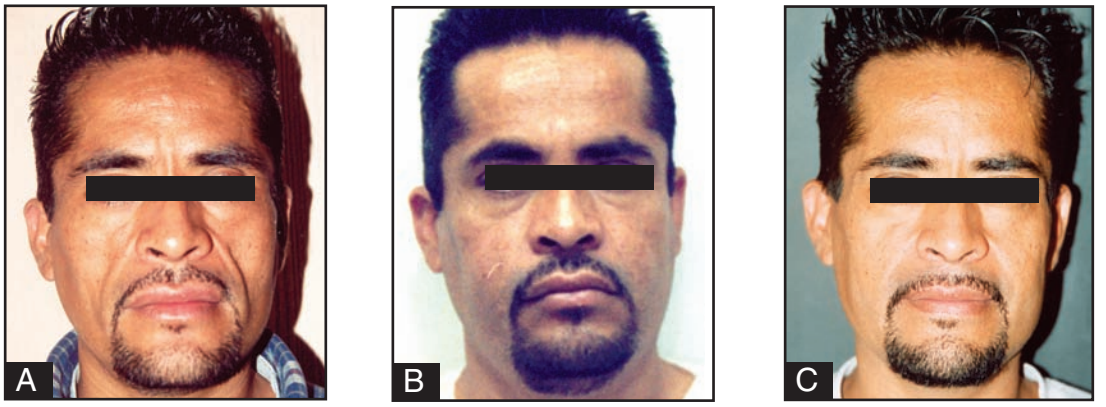
investigation, it was decided that a patient with moderate lipoatrophy required a fourth intervention and a patient with acute lipoatrophy required a fifth intervention.

All of the acute patients required four sessions except for one patient who required a fifth session. In contrast, most of the moderate patients required two sessions. Only nine patients required a third session and one patient required a fourth session, as seen in Table 2.

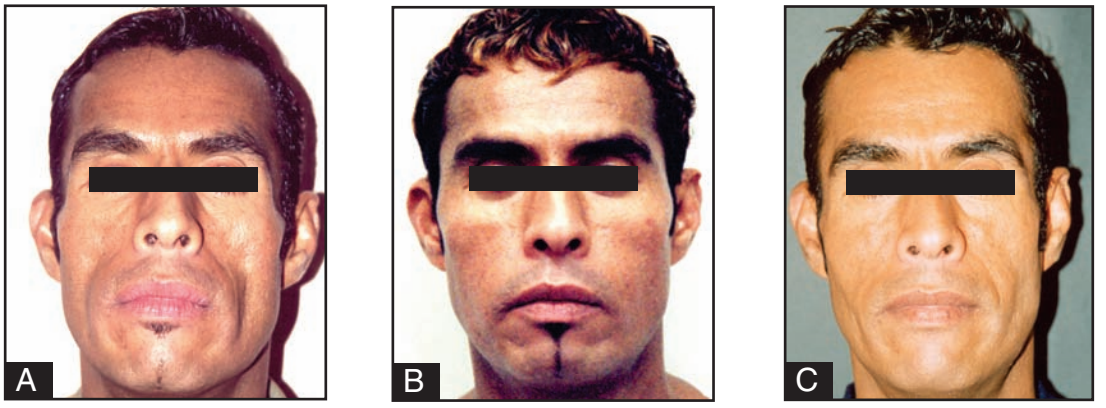
Materials. Each 100mg vial of the product used during the study contained glycolyic acid, polylactic acid,[10,11] HMC, D-mannitol, Tween 80, and PH stabilizer. Anesthetics used included topical Anestop (Pro-Medic) and local Xylocaine—2% lidocaine injectable solution without epinephrine (Astra Zeneca). Syringes and needles used included Plastipak BD 3mL (sterilized/disposable) and 23x25mm—26x25mm needles (Becton Dickinson de Mexico, SA de CV). Other materials used in the study included Protec surgical gloves (type 1, subtype B, sterilized, disposable), surgical mask type N95, hats, coats, glasses, disinfectants, and sterilization and treating materials.

Support institutions for the investigation's technical requirements were Pathology, Radiology, and Medical Facilities of the Del Prado Hospital and Medical Center in Tijuana, B. C., Unidad de Radiodiagnostico, SA de CV, Mexico City (radiology), and Axel & Hicks Laboratory, Mexico City (Pathological Anatomy and Dermal Pathology).

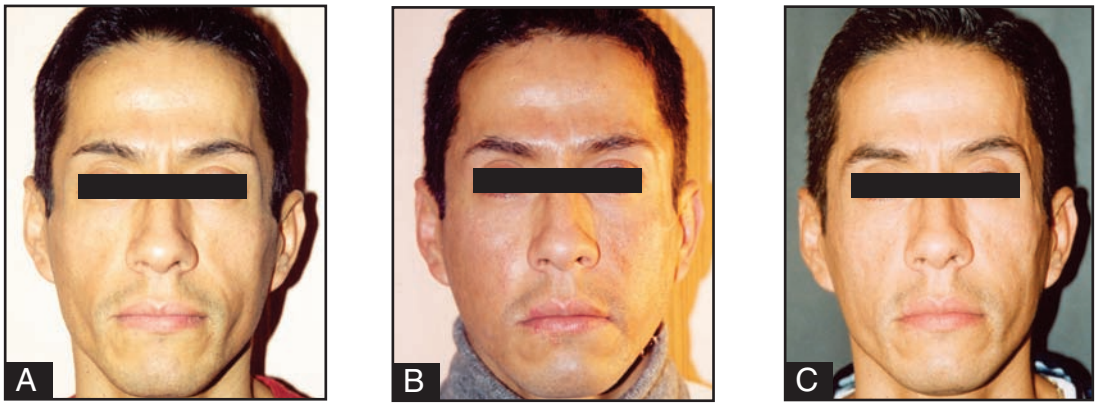
Procedure. The treatment program was divided between the three investigation team members. After scrubbing, the treating physicians used a lab coat, glasses or protective visor, surgical mask and cap, and sterilized surgical gloves (similar for assistant staff). The physician described the proceedings in general terms to the participant, explained the reactions that were possible, and asked the patient to freely express his feelings during the session and any time afterwards. The participant's face was cleaned in general (asepsis and anti-asepsis of the area to be treated with surgical soap and/or Isodine) and areas to be treated were pen-marked. Ice packs were applied for 3 to 5 minutes to provoke a superficial vasoconstriction. A topical anesthetic was used prior to applying the local anesthesia. All participants received either cutaneous or oral mucous local anesthesia or a nerve block. The product was reconstituted with 4mL of physiological saline solution (0.91% w/v of NaCl, about 300 mOsm), using a 5mL syringe with a 23x25mm needle (both Becton Dickinson). The vial was held at a slight angle and slowly turned until the 4mL of saline solution had been dispensed. The vial was then set to rest for five minutes after which the vial was vigorously shaken until a homogenous suspension had formed. The required amount of product was retrieved with the same syringe and needle. To inject the product into the patient, the 23x25mm needle was replaced with a 26x25mm needle (Becton Dickinson). The needles were replaced with new ones during the procedure, or as required. Injection



Figures 2A–2C. (A) The patient prior to treatment (September 12, 2002). The upper third shows a slight caving of the temporal and orbicular areas. The zygomatic area is starting to collapse and the inferior third shows a significant decline of the lower maxillary, producing a protruding fold in the nasal area (weight 64 kg). (B) The patient 91 days from his last session (February 10, 2003). The patient's weight had increased to 70kg (+6kg). Despite this weight gain, the treatment effects produced facial balance with the recovery of the temporal, zygomatic, and levator labii muscle support. (C) The patient on November 29, 2004. The subject's weight was down to 58.5kg, which is 5.5kg less than the recorded weight prior to the start of the program (Figure 3A). Two years after his last treatment, the effects of the product, although receding, continue to sustain an extraordinary overall facial balance.



Figures 3A–3C. (A) The patient prior to treatment (September 13, 2002). Significant caving of temples and slight depression of procerus area. Zygomatic area also affected by minor orbicular decline. The oral and mandible segments have the highest damage due to collapse of maxillary and masseter muscle. (B) The patient on February 13, 2003. At 93 days from last session the facial contour is balanced and harmony has been restored to the affected regions. (C) The patient on November 29, 2004. Two years from the last session, the facial contour sustains a favorable balance, although there is the visual evidence of deterioration, it is far from the state the subject presented prior to the start of treatment.



Figures 4A–4C. (A) The patient prior to treatment (September 12, 2002). Relative collapse of temples and slight periorbital depression. The mandibular region is the most affected by depressive sequel of the elevator and depressor muscles of the buccal angles. Dry and yellowish skin condition. (B) The patient 91 days after last session. All canons have been resolved satisfactorily, correcting the general facial balance with better skin hydration and facial pigmentation. (C) The patient on July 29, 2004. The effects of the treatment at 21 months were diminished by 90 percent in the temporal and periorbital regions. The depressive sequel of the elevator and depressor muscles at the buccal angles affect the mandibular region where 75 percent of the repairing effects have faded.

TABLE 3. Summary of side effects					
SESSION	**1A**	**2A**	**3A**	**4A**	
PARTICIPANTS	**30**	**30**	**23**	**14**	**Total**
Erythema	30	30	23	14	**97**
Ecchymosis	16	8	7	6	**37**
Edema					
Light	2	3	4	1	**10**
Mild	5	3	2	2	**12**
Major	2	1	–	–	**3**
Hematoma					
Light	2	1	3	1	**7**
Mild	3	2	1	–	**6**
Major	–	–	–	–	–
Adverse reactions	–	–	–	–	–
Complications	–	–	–	–	–
TOTAL	**60**	**48**	**40**	**24**	**172**

methodology is the key factor to achieve optimal results. The choice of the injection technique depends on the indication, its location, the filler substance, size of the needle, and the experience of the injector. Before proceeding to infiltrate the product, a reflux technique was performed every time to ensure that a vessel had not been punctured.

The following methods were used to infiltrate the product:

- *Tunnel method.* The needle is inserted at a given angle and to a desired depth, slowly pulling it back while pressing the plunger to leave a string-like deposit of a given amount of product. This method can be used at any of the three dermis levels.
- *Layered method*. Two deposits of product are infiltrated, one on top of the other using the tunnel method. This method is only possible at intermediate and deep levels of the dermis.
- *Delta method.* This method involves insertions that begin at one point and fan out or vice-versa. This method is most effective at $12^1/_4$ and $15^1/_4$ angles at superficial and intermediate levels.
- *Grill method.* This method involves cross insertions to increase volume in collapsed areas or model the facial oval. This method can be used at any of the three dermis levels.

Once the treatment of an area was completed, a light massage was applied to disseminate and consolidate the presence of the product, except in the lower palpebral area. An antibacterial unguent (Neosporin, Johnson and Johnson Consumer Products) was applied at each insertion point after wiping the area with sterile gauze. At the end of the overall session, ice pads were applied to the treated areas for periods of 15 to 20 minutes in a 3x3-minute sequence (application and rest). The syringe, needles, and disinfecting materials were destroyed at the end of the session in conformity with Good Clinical Practice.

RESULTS

Due to the metabolic characteristics of each participant, tissue response to the product's application varied depending on the degree of facial fat loss in the treatment area.

Pathology. A biopsy was performed on 10 patients. The investigators believe that the results were representative for all cases. Although a proliferation of myofibroblasts were initially identified in the biopsy material, these, or any other harmful scar processes, were not detected clinically in any of the patients. These biopsies demonstrated the aesthetic and reconstructive action of the product, devoid of adverse scar reactions or hypersensitivity reactions.

Microscopic description. Substantial changes of the affected regions were noticeable in all cases. A fibrosis development of foreign body reaction became evident in the pathological analysis (biopsies) in which the presence of new collagen is noticeable as shown in Figure 1.

Radiology analysis. During the study's initial phase and after the subcutaneous introduction of the product, transversal planes were performed on the nostril's lateral border and over the temporal regions, slightly out of the orbital border. The ultrasound registered a good cutaneous and subcutaneous increase.

Measures of aesthetic effectiveness. Figure 2 shows a patient who represents one of the best results obtained during the investigation; Figure 3 shows a patient who represents the average results obtained during the investigation; and Figure 4 shows a patient who represents one of the least lasting results obtained during the investigation.

Biological assimilation process analysis. Initially, the subcutaneously implanted hydroxyacetic and lactate-based formulation provoked a nonspecific mixed inflammatory cell infiltrate of foreign body type, in which the formulation acts as a relatively inert substance since it cannot be phagocytized by a single macrophage due to the size of the product's asymmetric particles (50µm–70µm). Thus, multinuclear giant cells are formed for this function.

The inflammatory response is not of the immune type (immune granuloma or tubercular type) in which the injected product's components would act as antigens, producing a specific immune response mediated by cells (type IV disorder in hypersensitivity reactions).

The body recognizes the similarity of the synthetic substitute, which is phagocytized and totally eliminated, provoking an "integrum" repair by connective tissue with scarce or nil retraction phenomena and even less of a pathological "contracture" process.

Although correction of skin deficiency is not made with the same type of tissue, the anomaly is repaired by restoring connective tissue, which increases volume as a response to an inflammatory process due to the effect of a foreign body

(caused by the polylactic segment of the implant). See Table 3 for side effects and Table 4 for a summary of discomfort or pain.

DISCUSSION

The distortion of horizontal proportions in nasal-orbital, ocular, naso-facial, and oral canons, as well as vertical proportions of the upper, middle, and lower thirds, define the loss in facial contour features, allowing a macro-optical grading of skin condition and facial harmony faults caused by the ravages of lipoatrophy syndrome.

These physiognomic elements deteriorate in time as a natural process of aging; however, physiognomic decline can also be caused by health disorders. Nonetheless, today both contingencies can be solved by plastic surgery or camouflage implants used by aesthetic medicine, such as the product under investigation, which represents for patients with a deteriorated skin condition and/or atrophic affliction of the subcutaneous fat layer, a more efficient and risk-free therapeutic and aesthetic alternative. Skin deterioration and lipoatrophy are not only the result of the natural aging process, they are also the result of sickness and certain medication, such as antiretroviral therapy.

In this study, the implant's efficiency was established as all patients registered considerable bulking of the cutaneous layers as well as improvement of the microscopic characteristics of the skin. This was evident by macro-optic appearance, which confirmed visually the substantial filling effects as treatment developed, particularly 90 days after the last intervention. The facial anatomical areas bordering high activity muscle groups due to gesticulation or mastication denoted a more effective recuperation than those areas with less muscular activity, which, nevertheless, showed highly satisfactory results in all cases.

TABLE 4. Summary of discomfort or pain source

SESSION	1A	2A	3A	4A
PARTICIPANTS	30	30	23	14
Due to the injection of anesthesia				
• Nil	4	5	3	2
• Moderate	16	20	19	12
• Painful	10	5	1	–
Due to the injection of product				
• Nil	23	30	22	14
• Moderate	7	–	1	–
• Painful	–	–	–	–
Due to the product (after the session and during the following five days or more)				
• Nil	1	19	18	9
• Moderate	17*	7	4	5
• Painful	12*	4	1	–

* The high incidence of "moderate and painful" symptoms attributed to the product during the first session was due to fading anesthesia effects and to the novelty in visual and tactile perception by the patient.

CONCLUSION

The results of this clinical investigation indicate that this product is a safe, reliable, and efficient device for treatment of deteriorated skin conditions and/or facial lipoatrophy. Externally, the product stimulates hydration and skin smoothness. Internally, it generates new collagen stimulated by both polylactic acid and glycolic acid, giving the skin a rejuvenated aspect, causing cutaneous layers to bulge and restoring facial contour without risks or adverse reactions, secondary complications, or any other pathological rejections. The authors conclude that the product investigated is a safe, efficient, reliable, long-lasting dermal filler for the treatment of deteriorated skin conditions and/or facial lipoatrophy.

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